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Published in:
Journal of Pain Research

DOI:
[10.2147/JPR.S138519](https://doi.org/10.2147/JPR.S138519)

Publication date:
2017

Document version
Publisher's PDF, also known as Version of record

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Citation for published version (APA):
Fabritius, M. L., Wetterslev, J., Mathiesen, O., & Dahl, J. B. (2017). Dose-related beneficial and harmful effects of gabapentin in postoperative pain management: post hoc analyses from a systematic review with meta-analyses and trial sequential analyses. *Journal of Pain Research*, 2017(10), 2547-2563.
<https://doi.org/10.2147/JPR.S138519>

Dose-related beneficial and harmful effects of gabapentin in postoperative pain management – post hoc analyses from a systematic review with meta-analyses and trial sequential analyses

Maria Louise Fabritius¹
Jørn Wetterslev²
Ole Mathiesen³
Jørgen B Dahl¹

¹Department of Anaesthesiology and Intensive Care, Bispebjerg and Frederiksberg Hospitals, Copenhagen, Denmark; ²Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen University Hospital, Copenhagen, Denmark; ³Department of Anaesthesiology, Zealand University Hospital, Køge, Denmark

Background: During the last 15 years, gabapentin has become an established component of postoperative pain treatment. Gabapentin has been employed in a wide range of doses, but little is known about the optimal dose, providing the best balance between benefit and harm. This systematic review with meta-analyses aimed to explore the beneficial and harmful effects of various doses of gabapentin administered to surgical patients.

Materials and methods: Data in this paper were derived from an original review, and the subgroup analyses were predefined in an International Prospective Register of Systematic Reviews published protocol: PROSPERO (ID: CRD42013006538). The methods followed Cochrane guidelines. The Cochrane Library's CENTRAL, PubMed, EMBASE, Science Citation Index Expanded, Google Scholar, and FDA database were searched for relevant trials. Randomized clinical trials comparing gabapentin versus placebo were included. Four different dose intervals were investigated: 0–350, 351–700, 701–1050, and >1050 mg. Primary co-outcomes were 24-hour morphine consumption and serious adverse events (SAEs), with emphasis put on trials with low risk of bias.

Results: One hundred and twenty-two randomized clinical trials, with 8466 patients, were included. Sixteen were overall low risk of bias. No consistent increase in morphine-sparing effect was observed with increasing doses of gabapentin from the trials with low risk of bias. Analyzing all trials, the smallest and the highest dose subgroups demonstrated numerically the most prominent reduction in morphine consumption. Twenty-seven trials reported 72 SAEs, of which 83% were reported in the >1050 mg subgroup. No systematic increase in SAEs was observed with increasing doses of gabapentin.

Conclusion: Data were sparse, and the small number of trials with low risk of bias is a major limitation for firm conclusions. Taking these limitations into account, we were not able to demonstrate a clear relationship between the dosage of gabapentin and opioid-sparing or harmful effects. These subgroup analyses are exploratory and hypothesis-generating for future trialists.

Keywords: gabapentin, 1-(aminomethyl)cyclohexanecarboxylic acid, analgesic, postoperative pain management, dose effect

Correspondence: Maria Louise Fabritius
Department of Anaesthesiology
and Intensive Care, Bispebjerg and
Frederiksberg Hospitals, Bispebjerg bakke
23, 2400 Copenhagen, Denmark
Tel +45 6017 9531
Email malou_fabritius@dadlnet.dk

Introduction

During the last 15 years, gabapentin has become an established component of postoperative analgesia. Gabapentin has been employed in a wide range of doses, but little is known about the optimal dose, providing the best balance between benefit and harm in postoperative pain treatment.

The number of published, dose-finding gabapentin trials in postoperative pain treatment is limited,^{1–11} and the results are inconsistent. It is well established, however, that oral gabapentin is absorbed in part by diffusion and in part by a carrier-mediated saturable transport mechanism system.¹³ Thus, the bioavailability of oral gabapentin is not linear, but inversely dependent on the dose,¹⁴ ranging from ~60% for a 300 mg dose to ~30% with doses of 1600 mg.^{14–16}

Consequently, the optimal dosing of gabapentin, providing the best balance between benefit and harm, may not be obvious. In this post hoc subgroup analysis, we aimed to explore the relative effects of different doses of gabapentin on 24-hour morphine consumption, pain intensity, risk of serious adverse events (SAEs), and other adverse events.

We hypothesized that increasing doses of gabapentin would lead to increased reduction in 24-hour morphine consumption and/or pain intensity, decreased adverse effects, and probably also increased risk of SAEs and other drug-specific adverse events. We realized, however, that the possible increase in beneficial and harmful effects with increasing doses of gabapentin would probably not be linear due to the nonlinear bioavailability of oral gabapentin.

Materials and methods

This review includes exploratory post hoc analyses from an original systematic review, employing the Cochrane Collaboration methodology. The protocol of the original PRISMA-compliant review is published in the International Prospective Register of Systematic Reviews website (www.crd.york.ac.uk/PROSPERO) with the registration no. CRD42013006538.¹⁷

Literature search

Our comprehensive search strategy was planned by a trial search coordinator and reported in the published systematic review¹⁸ and [Supplementary material S1](#): search strategies.

The Cochrane Library's CENTRAL, PubMed, EMBASE, Science Citation Index Expanded, Google Scholar, and FDA database, and reference lists of trials were searched for relevant trials. Unpublished trials were searched in relevant databases.

Randomized clinical trials comparing gabapentin versus placebo, irrespective of publication type, status, publication year, and language, were included. All non-English articles were translated to English. We updated the search strategy on April 12, 2016.

Data

MLF and one of the independent authors (AG, MSH, PLP, LN) screened the titles and abstracts, evaluated the risk of bias, and extracted data. Extracted data included article publication year, number of participants, surgical procedure, follow-up period and gabapentin dose administered, consumption of morphine (intravenous morphine based on equivalency, [Supplementary material S2](#)) and other nonopioid analgesics, pain intensity, and any adverse effects reported, including SAEs.

Pain intensity was reported in different scales in the original trials. All pain intensity scales using intensity scores between 0 and 10 were converted to the visual analog scale (VAS) 0–100 mm.

If data were incomplete or bias assessment was unclear, the corresponding author was contacted. This contact was repeated after 2 weeks in case of no response to initial contact. If the corresponding author did not reply, the involved bias domains were classified as unclear.

Assessment of risk of bias

The risk of bias assessment adhered to the Cochrane Handbook methodology.²⁰ All the included trials were assessed as low, unclear, or high risk of bias using the six bias domains described in the handbook. The “other” bias domain consisted of financial and confirmatory bias evaluations.²¹ Any difference in evaluations between authors on any part of the data extraction and evaluations process was solved by OM, JBD, or JW.

It was protocolled that the review and conclusions would primarily be based on trials with low risk of bias.

Small trial size

This post hoc analysis assessed the number of patients included in each original trial as defined in the original systematic review.¹⁸ Trials with less than 50 participants were defined as small trials, trials with more than 50 participants in each group formed the second group, and the trials with more than 200 participants made up the final group.

Analyses

The dose treatments of gabapentin were divided into four groups: 0–350, 351–700, 701–1050, and more than 1050 mg. The defined groups represent the four most commonly used dose treatments in gabapentin research, which are 300, 600, 900, and 1200 mg.

All doses are considered as 24-hour treatments, regardless of single or multiple administrations, pre- or postoperative treatments, or the duration of the treatment.

If an original trial investigated more than one dose, the control group receiving placebo was divided into the corresponding number of intervention groups. The trials in which the divided control groups included less than 20 participants were excluded. The individual dose-finding trials were counted as one trial in all summary statistics. Whenever the trials were included in cumulative analyses, the trials were viewed as separate trials.

Outcomes

Twenty-four-hour morphine consumption represented the beneficial primary outcome, and SAEs represented the harmful primary outcome. SAEs were classified according to the International Conference of Harmonization – Good Clinical Practice definitions: medical events being either life-threatening, resulting in death, disability, or significant loss of function, or causing hospital admission or prolonged hospitalization.¹⁸

The secondary outcomes were divided into beneficial outcomes: reduction in early (6-hour) and late (24-hour) pain postoperatively, both at rest and during mobilization, and harmful outcomes: all other adverse events.

Statistical analysis

Review Manager (RevMan; computer program), Version 5.1.6 was used in the cumulated analyses and subgroup analyses.

The handling of median and range (or interquartile range), longer ordinal scales, and dichotomous data, examination of heterogeneity, employment of fixed- or random-effect models, Peto's odds ratio (OR), and handling of few and rare events were done according to the International Prospective Register of Systematic Reviews published protocol and is described in the published PRISMA-compliant systematic review.^{17,18}

If more than one trial was included in the outcome, the estimates were pooled in meta-analyses and test for subgroup analyses was performed using RevMan in which the method to test for subgroup differences was implemented.

All trials with one intervention group and one control group were included. Handling of trials investigating more than one dose is described above. The mean and standard deviations were divided according to the methodology described in the Cochrane Handbook.^{20,22}

Trial sequential analysis (TSA) was used to adjust for sparse data and repetitive testing in the cumulative analyses.^{23,24} Minimal relevant clinical differences were defined as in the published systematic review.¹⁸ TSA is only

reported if the accrued information size was 5% or more of the required information size (RIS), since the TSA program is only able to report trial sequential monitoring boundaries if this is the case.

Results

In the original published systematic review, 19,137 titles were located, and after removal of duplicates, 16,303 titles were screened for inclusion and exclusion criteria. The original systematic review included 135 randomized clinical trials, including 3 observational studies.¹⁸

For the purpose of this review, the 3 observational studies, and 10 dose-finding trials with less than 20 patients in the split control groups, were excluded,^{1–4,6,7,8,10,11,25} leaving 122 trials with 8466 participants for analyses ([Supplementary material S3: trial characteristics](#)).^{5,9,19,25–143}

Trial characteristics

In these analyses, 16 trials demonstrated overall low risk of bias,^{5,9,35,41,55,58,62,76,91,95,107,108,127,128,140} 36 trials showed unclear risk of bias,^{25,26,30,32,34,36,38,40,42,45,51,52,54,57,59,67,69,70,73–75,79,84,86,88,99,100,101,103,119,122,124,125,130,139,141,143}, and 70 showed high risk of bias (Figure 1; [Supplementary material S4: risk of bias graph](#)).^{6,8,12,19,27–29,31,33,37,39,43,44,46–50,53,56,60,61,63–66,71,72,77,78,80–83,85,87,88,90,92–94,97,99,102,105,106,109–118,120,121,123,124,126,129,131,132,134–138,142}

We found that 105 trials were “small trials”,^{12,25–27,29–43,45,47–61,63,65–75,77–84,86–94,96–101,104–106,109–127,131–142} 14 trials included more than 50 participants in each group,^{9,19,28,44,46,62,76,85,95,107,108,128,130,143} and only 2 trials included more than 200 participants.^{5,102}

Treatment with gabapentin included both single-dose (84 trials)^{9,12,25–29,31–36,40–45,47,49–52,56,58,59,61,63,65–67,69–73,75–78,82–86,88,90–94,96,97,99,102–106,109,111–118,120–122,124,125,128–131,133,136,138,139,143} and multiple-dose administration (38 trials).^{5,30,37–39,46,48,53–55,57,60,62,68,74,79–81,89,95,98,100,101,107,108,110,119,123,126,127,132,134,135,137,140–142}

For further information about the individual trials, see [Supplementary material S3: trial characteristics](#).

Primary outcomes

Total 24-hour morphine consumption

Sixty-five trials with 4851 patients reported 24-hour opioid consumption, and 15 trials (1318 participants) were classified as overall low risk of bias.

Trials with low risk of bias

In the 0–350 mg subgroup, a reduction in 24-hour morphine consumption of 2.2 mg (0.1, 4.4; $p=0.04$)^{9,140} was reported with gabapentin versus control. The 351–700 mg

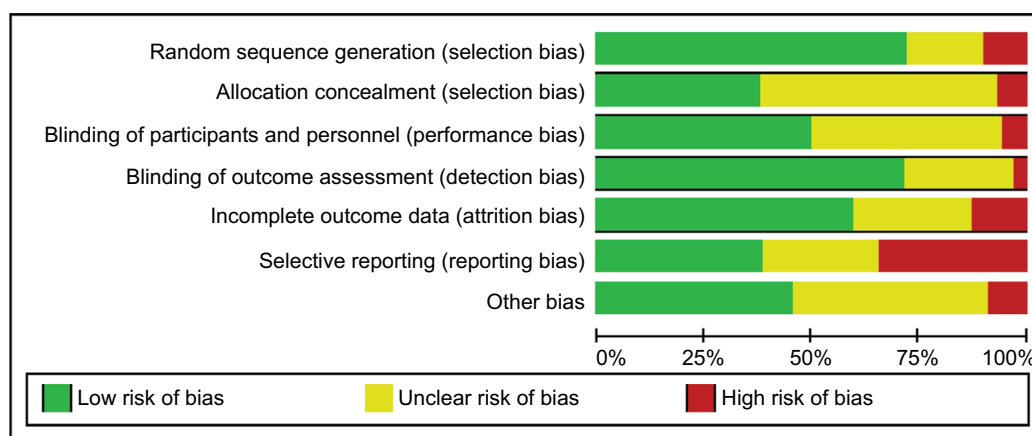


Figure 1 Bias evaluation of the six bias domains.

Note: The “other” bias domain consists of an evaluation of financial and confirmatory bias.

subgroup demonstrated a reduction of 3.4 mg (0.9, 8.5; $p=0.12$),^{9,91,95,96,107,108,128} the 701–1050 mg subgroup an increase in consumption of 24-hour morphine consumption of 1.1 mg (0.3, 2.0; $p=0.01$),^{5,41,55,58,62} and the subgroup >1050 mg reported a reduction of 2.9 mg (–1.1, 6.9; $p=0.2$), as shown in Table 1 and Figure 2.^{5,41,55,62}

The test for subgroup differences was significant for the 701–1050 mg subgroup compared with the other subgroups ($p=0.002$), but no systematic increase in morphine-sparing effect was observed with increasing doses of gabapentin. With TSA, half the subgroup meta-analyses reached the futility area with the predefined minimal clinical difference and alpha and beta, while the other half did not report firm results (Table 1).

All trials

All subgroups demonstrated a reduction in 24-hour morphine consumption (Table 2 and Figure 3). Differences between the different dose intervals were statistically significant in test for subgroup differences between the 350–700, 701–1050 mg, and >1050 mg subgroups. The 0–350 mg subgroup and the >1050 mg subgroup demonstrated numerically most pronounced reduction in morphine consumption, but no systematic increase in morphine-sparing effect was observed with increasing doses of gabapentin. Only the meta-analysis for the subgroup 701–1050 did not report firm evidence according to TSA (Table 1).

SAE

Twenty-seven trials with 1958 participants reported 72 SAEs, of which 83% were reported in the >1050 mg subgroup. Of the 27 trials, 8 were classified as overall low risk of bias,^{5,9,41,62,76,107,128,140} and these 8 trials reported more than half

the SAEs. The trials with overall low risk of bias reported the following SAEs: death, vein thrombosis, pneumonia, wound infection, admission to intensive care unit, and prolonged hospital stay.

Trials with low risk of bias

In the 0–350 mg subgroup,^{9,140} Peto's OR and TSA were not estimable. In the remaining subgroups, the risk of SAEs was: 351–700 mg subgroup: OR 0.9 (0.2, 3.4; $p=0.85$)^{9,76,107,128}; 700–1050 mg subgroup: OR 0.6 (0.04, 8.6; $p=0.70$)⁵; and >1050 mg subgroup: OR 2.0 (0.9, 4.5; $p=0.1$).^{5,41,62} No subgroup differences were demonstrated for this outcome, and no systematic increase in SAEs was observed with increasing doses of gabapentin (Figure 4). It was only possible to conduct TSA on two subgroups (351–700 and >1050 mg), and both subgroups had less than 20% of RIS and none reported firm evidence (Table 1).

All trials

None of the gabapentin subgroups demonstrated statistically significant increases in SAEs compared with controls (Figure 5). No significant differences between the different dose intervals were demonstrated, and no systematic increase in SAEs was observed with increasing doses of gabapentin (Table 2). TSA showed that none of the three subgroups, 351–700, 701–1050, and >1050 mg, reached firm evidence, nor did they reach more than 5% of RIS.

Secondary outcomes

Pain intensity

Little data have been reported from trials with low risk of bias, limiting the reliability of the test for subgroup differences. No consistent dose-related trends or subgroup

Table 1 The estimates on primary outcomes from trials with low risk of bias and from all trials despite risk of bias

Surgical procedure	Dose (mg)		351–700		701–1050		> 1050	
	0–350	701–1050	351–700	701–1050	> 1050	351–700	701–1050	> 1050
Outcomes	Reduction (mg) MD or Peto's OR estimate (95% CI; p-value; trials; participants; TSA adj. CI; accrued percentage of required information size)	Test for subgroup difference p-value	Reduction (mg) MD or Peto's OR estimate (95% CI; p-value; trials; participants; TSA adj. CI; accrued percentage of required information size)	Test for subgroup difference p-value	Reduction (mg) MD or Peto's OR estimate (95% CI; p-value; trials; participants; TSA adj. CI; accrued percentage of required information size)	Test for subgroup difference p-value	Reduction (mg) MD or Peto's OR estimate (95% CI; p-value; trials; participants; TSA adj. CI; accrued percentage of required information size)	Test for subgroup difference p-value
Beneficial outcomes								
24-hour morphine consumption	2.2 mg (0.1, 4.4; p=0.04; 2 trials; 111 participants; TSA adj. CI: 0.1, 4.6; 191%)	p=0.69	3.4 mg (0.9, 7.7; p=0.12; 7 trials; 700 participants; TSA adj. CI: -3.3, 11.6; 44%)	p=0.33	-1.1 mg (-0.3, -2.0; p=0.01; 2 trials; 181 participants; TSA adj. CI: 0.3, 2.0; 329%)	p=0.002	2.9 mg (1.1, 6.9; p=0.2; 4 trials; 326 participants; TSA adj. CI: -1.4, 5.6; 89.6%)	p=0.9
24-hour morphine consumption	8.0 mg (6.2, 9.8; p<0.00001; 11 trials; 1070 participants; TSA adj. CI: 6.2, 9.8; 263.5%)	p=0.25	4.6 mg (3.1, 6.1; p<0.0001; 20 trials; 1811 participants; TSA adj. CI: 3.1, 6.1; 389%)	p=0.004	2.6 mg (-1.4, 6.6; p=0.2; 7 trials; 375 participants; TSA adj. CI: -2.9, 8.2; 57.5%)	p=0.03	9.0 mg (7.1, 10.9; p<0.00001; 27 trials; 1595 participants; TSA adj. CI: 7.2, 11; 245.6%)	p=0.02
Harmful outcomes								
Serious adverse events	Not estimable (2 trials, 113 participants)	-	0.9 (0.2, 3.4; p=0.85; 4 trials; 404 participants; TSA adj. CI: 0.0, 220.8; 18.1%)	p=0.44	0.6 (0.04, 8.6; p=0.70; 1 trial; 121 patients; TSA adj. -)	p=0.52	2.0 (0.9, 4.5; p=0.1; 3 trials; 287 participants; TSA adj. CI: 0.1, 40.0; 17.8%)	p=0.29
Serious adverse events	Not estimable (3 trials, 179 participants)	-	0.9 (0.2, 3.4; p=0.85; 8 trials; 682 participants; TSA adj. CI: 0.1, 11.7; 22.9%)	p=0.44	0.6 (0.04, 8.6; p=0.70; 3 trials; 221 participants; TSA adj. CI: <5%)	p=0.52	1.3 (0.8, 2.4; p=0.33; 13 trials; 876 participants; TSA adj. CI: 0.6, 3.6; 44.4%)	p=0.29

Abbreviations: MD, mean difference; OR, odds ratio; TSA, trial sequential analysis.

Table 2 The beneficial secondary outcomes from trials with low risk of bias and all trials

Beneficial outcomes	0-350 mg			351-700 mg			701-1050 mg			> 1050 mg		
	Reduction (mm) MD Estimate (95% CI; p-value; trials; TSA adj. CI; accrued percentage of required information size)	Test for subgroup difference p-value	MD Estimate (95% CI; p-value; trials; TSA adj. CI; accrued percentage of required information size)	Test for subgroup difference p-value	Reduction (mm) MD Estimate (95% CI; p-value; trials; TSA adj. CI; accrued percentage of required information size)	Test for subgroup difference p-value	Reduction (mm) MD Estimate (95% CI; p-value; trials; TSA adj. CI; accrued percentage of required information size)	Test for subgroup difference p-value	Reduction (mm) MD Estimate (95% CI; p-value; trials; TSA adj. CI; accrued percentage of required information size)	Test for subgroup difference p-value	Reduction (mm) MD Estimate (95% CI; p-value; trials; TSA adj. CI; accrued percentage of required information size)	Test for subgroup difference p-value
6-hour VAS at rest	6.4 mm (-1.9, 11.0; p=0.006; 2 trials; 111 participants; TSA adj. CI: -5.8, 11.4; 73%)	p=0.98	13.2 mm (-1.1, 27.6; p=0.07; 3 trials; 289 participants; TSA adj. CI: -28.5, 55.0; 17.8%)	p=0.23	-	-	5.6 mm (0.5, 10.7; p=0.03; 3 trials; 206 participants; TSA adj. CI: -0.8, 11.9; 141%)	-	-	-	-	-
6-hour VAS at rest	13.7 mm (7.1, 20.0; p<0.0001; 10 trials; 740 participants; TSA adj. CI: 7.1, 20.0; 83.7%)	p=0.53	15.3 mm (10.7, 20.0; p<0.0001; 18 trials; 1275 participants; TSA adj. CI: 10.7, 20.0; 175%)	p=0.05	6.0 mm (2.7, 9.3; p=0.0003; 7 trials; 294 participants; TSA adj. CI: 0.9, 11.1; 330%)	p=0.006	9.4 mm (5.6, 13.3; p<0.0001; 27 trials; 1519 participants; TSA adj. CI: 5.6, 13.3; 241.1%)	-	-	-	-	-
6-hour VAS at mobilization	11 mm (5.7, 16.3; p<0.0001; 1 trial; 63 participants; TSA adj. CI: -)	-	12.4 mm (8.0, 16.8; p<0.0001; 3 trials; 227 participants; TSA adj. CI: 8.0, 16.1; 258%)	p=0.16	-	-	3.8 mm (-7.9, 15.4; p=0.53; 3 trials; 206 participants; TSA adj. CI: -21.1, 28.6; 26.8%)	-	-	-	-	-
6-hour VAS at mobilization	11.1 mm (5.8, 16.4; p<0.0001; 2 trials; 95 participants; TSA adj. CI: -13.1, 19.7; 130.1%)	p=0.30	10.2 mm (5.7, 14.7; p<0.0001; 6 trials; 438 participants; TSA adj. CI: 5.1, 15.3; 176.6%)	p=0.24	6.1 mm (-3.9, 16.2; p=0.23; 3 trials; 121 participants; TSA adj. CI: -2.2; 24.4; 36.1%)	p=0.67	6.3 mm (3.1, 9.6; p=0.0001; 15 trials; 898 participants; TSA adj. CI: 3.1, 9.6; 342.7%)	-	-	-	-	-
24-hour VAS at rest	0.6 mm (-3.0, 4.2; p=0.75; 2 trials; 107 participants; TSA adj. CI: -)	p=0.02	3.9 mm (-0.1, 7.9; p=0.05; 5 trials; 526 participants; TSA adj. CI: -0.1, 7.9; 268%)	p=0.005	-	-	1.8 mm (-3.4, 7.0; p=0.51; 4 trials; 331 participants; TSA adj. CI: -3.7; 7.2%)	-	-	-	-	-
24-hour VAS at rest	7.3 mm (1.7, 12.8; p=0.01; 13 trials; 806 participants; TSA adj. CI: 1.7, 12.8; 115.9%)	p=0.77	8.9 mm (4.8, 12.9; p<0.0001; 15 trials; 1315 participants; TSA adj. CI: 4.8, 12.9; 224.8%)	p=0.19	2.2 mm (-1.1, 5.6; p=0.19; 7 trials; 255 participants; TSA adj. CI: -1.7, 6.2; 318.8%)	p=0.02	6.1 mm (2.5, 9.7; p=0.0009; 27 trials; 1493 participants; TSA adj. CI: 2.5, 9.7; 280.6%)	-	-	-	-	-
24-hour VAS at mobilization	-2.0 mm (7.2, 11.2; p=0.67; 1 trial; 63 participants; TSA adj. CI: -)	-	5.9 mm (-0.9, 12.8; p=0.09; 5 trials; 526 participants; TSA adj. CI: -2.4, 14.3; 74%)	p=0.16	-1.0 mm (-3.3, 5.3; p=0.65; 1 trial; 121 participants; TSA adj. CI: -)	-	0.8 mm (-2.9, 4.5; p=0.67; 4 trials; 326 participants; TSA adj. CI: -2.7, 4.3; 300%)	-	-	-	-	-
24-hour VAS at mobilization	-1.0 mm (-7.9, 9.8; p=0.8; 2 trials; 95 participants; TSA adj. CI: -13.1, 15.0; 46.1%)	p=0.27	2.5 mm (-6.4, 11.4; p=0.58; 9 trials; 843 participants; TSA adj. CI: -17.4, 11.3; 17.4; 45.1%)	p=0.59	5.1 mm (-5.4, 15.5; p=0.34; 2 trials; 141 participants; TSA adj. CI: -14.6, 24.8; 33%)	p=0.92	5.9 mm (-1.5, 10.3; p=0.009; 15 trials; 922 participants; TSA adj. CI: -3.6, 10.9; 87.0%)	-	-	-	-	-

Abbreviations: CI, confidence interval; MD, mean difference; TSA, trial sequential analysis; VAS, visual analog scale.

differences were demonstrated in the all trials estimates (Table 2; [Supplementary material](#) S5–S12: forest plots of pain intensities).

Adverse events

No consistent dose-related trends or subgroup differences were demonstrated either in data from trials with low risk of bias or in the all trials estimates (Table 3). None of the meta-analyses of trials with low risk of bias reporting risk of AE reached firm evidence according to TSA ([Supplementary material](#) S13–S20: forest plot of AE).

Discussion

In this review, we aimed to explore the effect of increasing doses of gabapentin on postoperative morphine consumption, SAEs, pain intensity, and adverse events in four groups of trials that included the most commonly used doses of gabapentin for perioperative pain management: 300, 600, 900, and 1200 mg.

For the primary beneficial outcome, 24-hour morphine consumption, no consistent increase in morphine-sparing effect was observed with increasing doses of gabapentin, either in the analysis of trials with low risk of bias or in the all trials analysis. On the contrary, the smallest (0–350 mg) and the largest (>1050 mg) dose regimens demonstrated comparable and the most pronounced reduction in morphine consumption in the all trials analysis.

Only few SAEs were reported, limiting any reliable conclusion on this outcome. Of 72 stated SAEs, 83% were reported in the >1050 mg subgroup, indicating an increased risk of SAEs with increasing doses. Of the 27 trials reporting SAEs, 10 were classified as overall low risk of bias, and these 10 trials reported more than half the SAEs.

For the secondary outcomes, pain intensity and adverse events, no consistent dose-related trends or subgroup differences were demonstrated, either in data from trials with low risk of bias or in the all trials estimates.

We could not find any clear indication of a dose-related effect of gabapentin. A possible explanation may be the fact that higher doses of gabapentin lead to relatively smaller increases in blood concentrations because of the saturable absorption of gabapentin after oral administration.^{14,15,145} This may potentially provide an upper limit to the effect of beneficial outcomes and adverse events. However, none of our results indicated a clear upper limit or difference between subgroups, confirming this hypothesis. The nonlinear absorption may be the main reason of the less-predictable clinical

effect of increased doses, but other explanations also have to be considered.

The analgesic effect of gabapentin is considered to be related to its antihyperalgesic properties, as demonstrated for both single and multiple dosing in human volunteer pain models.^{146,147} In such models, gabapentin did not affect nociceptive pain per se.^{146–148} Furthermore, gabapentin demonstrated dose-dependent antihyperalgesic effects in rat pain models,¹⁴⁹ which, however, has not been investigated in humans. It is, therefore, unknown if increasing doses of gabapentin display increasing antihyperalgesic effects in humans, and if such a dose–response relationship is linear. This may contribute significantly to the shortcoming of detecting a dose–response effect in postoperative pain patients. Furthermore, postoperative pain is related to multiple pain mechanisms, of which hyperalgesia is only one. It is, though, unknown how important the hyperalgesic component is for the total sum of experienced pain. This may, in part, also explain the shortcomings of detecting a dose–response relationship for postoperative gabapentin treatment.

The optimal dose for postoperative pain treatment has been investigated in a few original clinical trials.^{2–11,143} The study by Van Elstraete et al¹⁵⁰ found a relatively high median effective analgesic dose of 21.7 mg/kg gabapentin in spinal fusion surgery. Considering this result, it is possible that the investigated doses, in general, are too low for analgesic efficacy, although higher doses (>1200 mg) most likely will produce profound adverse effects.

Most included trials were small in size, and 86% of the trials included less than 50 participants in each group, which can be a limitation. The large number of small-sized trials leads to repetitive testing in the cumulative meta-analyses, increasing the risk of random error. Accordingly, we applied TSA to compensate for this limitation. The majority of cumulative subgroup analyses of trials with low risk of bias did not reach firm evidence, or the RIS. This limits any firm evidence and conclusions. In addition, the lack of data may cause a type II error.

The strengths of these subgroup analyses are related to the primary systematic review that was carried out using Cochrane methodology and reported according to PRISMA guidelines. All trials were critically assessed using the Cochrane bias evaluation tools, and the risk of random error was assessed using TSA to adjust for sparse data and repetitive testing.

However, there are substantial limitations to our results. The conclusions based on our results are generally weakened

Table 3 The harmful secondary outcomes from trials with low risk of bias and all trials

Harmful outcomes	0-350 mg	351-700 mg	701-1050 mg	> 1050 mg
	RR Estimate (95% CI; p-value; trials; participants; TSA adj. CI; accrued percentage of required information size)	RR Estimate (95% CI; p-value; trials; participants; TSA adj. CI; accrued percentage of required information size)	RR Estimate (95% CI; p-value; trials; participants; TSA adj. CI; accrued percentage of required information size)	RR Estimate (95% CI; p-value; trials; participants; TSA adj. CI; accrued percentage of required information size)
Nausea	-	0.8	-	0.7
Low risk of bias	-	(0.4, 1.6; p=0.54; 3 trials; 218 participants; TSA adj. CI: 1.9, 15.6; 72.9%)	-	(0.5, 0.9; p=0.02; 2 trials; 180 participants; TSA adj. CI: 0.1, 1.2; 33.7%)
Nausea	0.9	0.8	0.8	0.8
All trials	(0.7, 1.1; p=0.16; 9 trials; 633 participants; TSA adj. CI: 0.7, 1.1; 70.6%)	(0.6, 1.1; p=0.10; 15 trials; 1019 participants; TSA adj. CI: 0.5, 1.3; 40.0%)	(0.5, 1.4; p=0.51; 4 trials; 271 participants; TSA adj. CI: 0.1, 7.2; 12.8%)	(0.6, 0.9; p=0.003; 21 trials; 1203 participants; TSA adj. CI: 0.3, 1.8; 50.4%)
Vomiting	-	2.0	-	1.0
Low risk of bias	-	(0.5, 7.3; p=0.3; 1 trial; 46 participants; TSA adj. CI: -)	-	(0.7, 1.6; p=0.85; 2 trials, 180 participants; TSA adj. CI: 0.2, 5.9; 16.5%)
Vomiting	0.8	0.7	0.7	0.8
All trials	(0.6, 1.2; p=0.26; 9 trials; 538 participants; TSA adj. CI: 0.4, 1.7; 29.2%)	(0.5, 0.9; p=0.007; 14 trials; 948 participants; TSA adj. CI: 0.4, 1.1; 54.8%)	(0.1, 3.7; p=0.64; 2 trials; 111 participants; TSA adj. CI: 0.1, 7.2; 12.8%)	(0.7, 1.1; p=0.002; 19 trials; 1188 participants; TSA adj. CI: 0.1, 6.1; 71.4%)
Sedation	1.2	1.0	0.8	1.6
Low risk of bias	(0.8, 1.6; p=0.4; 2 trials; 107 participants; TSA adj. CI: 0.3, 4.2; 15.2%)	(0.9, 1.3; p=0.69; 4 trials; 385 participants; TSA adj. CI: 0.4, 1.1; 54.8%)	(0.4, 1.6; p=0.59; 1 trial; 60 participants; TSA adj. CI: -)	(1.0, 2.5; p=0.05; 2 trials; 180 participants; TSA adj. CI: 0.2, 9.9; 12.4%)
Sedation	2.5	1.0	1.9	1.3
All trials	(0.9, 7.1; p=0.08; 8 trials; 734 participants; TSA adj. CI: <5%)	(0.8, 1.2; p=0.97; 15 trials; 1317 participants; TSA adj. CI: 0.8, 1.2; 98.7%)	(0.4, 8.7; p=0.43; 4 trials; 240 participants; TSA adj. CI: <5%)	(1.0, 1.6; p=0.02; 15 trials; 942 participants; TSA adj. CI: 0.9, 1.9; 41.7%)
Dizziness	1.2	1.0	0.8	1.0
Low risk of bias	(0.6, 2.5; p=0.57; 2 trials; 107 participants; TSA adj. CI: 0.1, 26.5; 5.8%)	(0.7, 1.3; p=0.77; 3 trials; 341 participants; TSA adj. CI: 0.5, 1.8; 28.9%)	(1.1, 60.1; p=0.04; 1 trial; 60 participants; TSA adj. CI: -)	(0.9, 1.3; p=0.68; 3 trials; 239 participants; TSA adj. CI: 0.7, 1.7; 21.9%)
Dizziness	0.8	1.0	3.0	1.2
All trials	(0.5, 1.3; p=0.45; 12 trials; 1209 participants; TSA adj. CI: 0.2, 4.4; 14.6%)	(0.8, 1.2; p=0.89; 13 trials; 1101 participants; TSA adj. CI: 0.7, 1.3; 64.8%)	(0.8, 11.2; p=0.10; 6 trials; 312 participants; TSA adj. CI: <5%)	(1.0, 1.5; p=0.11; 21 trials; 1400 participants; TSA adj. CI: 0.9, 1.2; 87.2%)

Abbreviations: CI, confidence interval; RR, relative risk; TSA, trial sequential analysis.

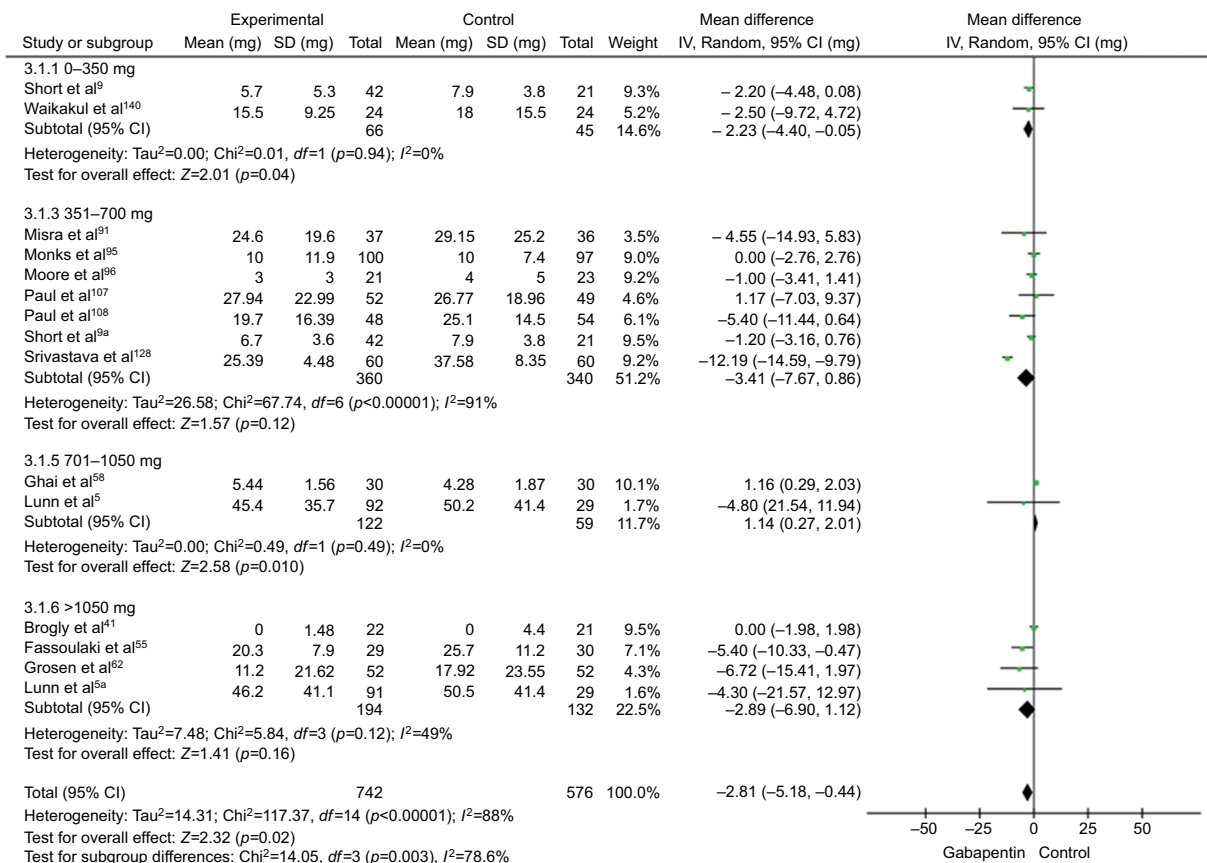


Figure 2 Forest plot of 24-hour morphine consumption from trials with overall low risk of bias.

Abbreviations: *df*, degrees of freedom; CI, confidence interval; SD, standard deviation; IV, inverse variance.

by the low number of trials classified as overall low risk of bias, which limits the test for subgroup differences, and pooled estimates in meta-analyses. The few number of trials with low risk of bias means that all trials estimates must be factored into the evaluation and interpretation of these subgroup analyses. It is well described that estimates from trials with unclear and high risk of bias have an inherent risk of overestimating beneficial outcomes and underestimating harmful events, which must be taken into account upon conclusions and further use in future hypothesis based on these analyses.¹⁴⁴

Few of the included trials reported SAEs, and most of the trials exhibited a short follow-up period, further limiting the analyses exploring the risks of gabapentin treatment.¹⁸

Further, this review consists of post hoc analyses, which limit the reliability of the results. The subgroups of our analyses must be interpreted as observational studies, with the inherent limitations of such studies: Confounding by other study characteristics may bias the analyses. Some of these study characteristics, such as gabapentin with other non-opioid analgesics, have been explored in the original work,¹⁸ while the effect of gabapentin in six different procedures was

explored in a separate published article finding no difference between surgical procedures on beneficial and harmful outcomes from trials with overall low risk of bias.¹⁵¹

Our post hoc analysis was meant to explore the dose effect of gabapentin in published randomized clinical trials, since there is no previously published systematic on the topic. Based on the combined analyses, we cannot recommend a specific dose or regimen, if any, for perioperative gabapentin treatment. We hope that our analyses may inspire the hypotheses of future trials.

Conclusion

Data were sparse in all subgroups, and the small number of trials with low risk of bias is a major limitation for firm conclusions. Taking these limitations into account, we were not able to demonstrate a clear relationship between the dosage of gabapentin and opioid-sparing or harmful effects. Numerically, most SAEs were reported in the higher dosing groups, and trials with low risk of bias reported the most SAEs. These subgroup analyses are exploratory and hypothesis-generating for future trialists.

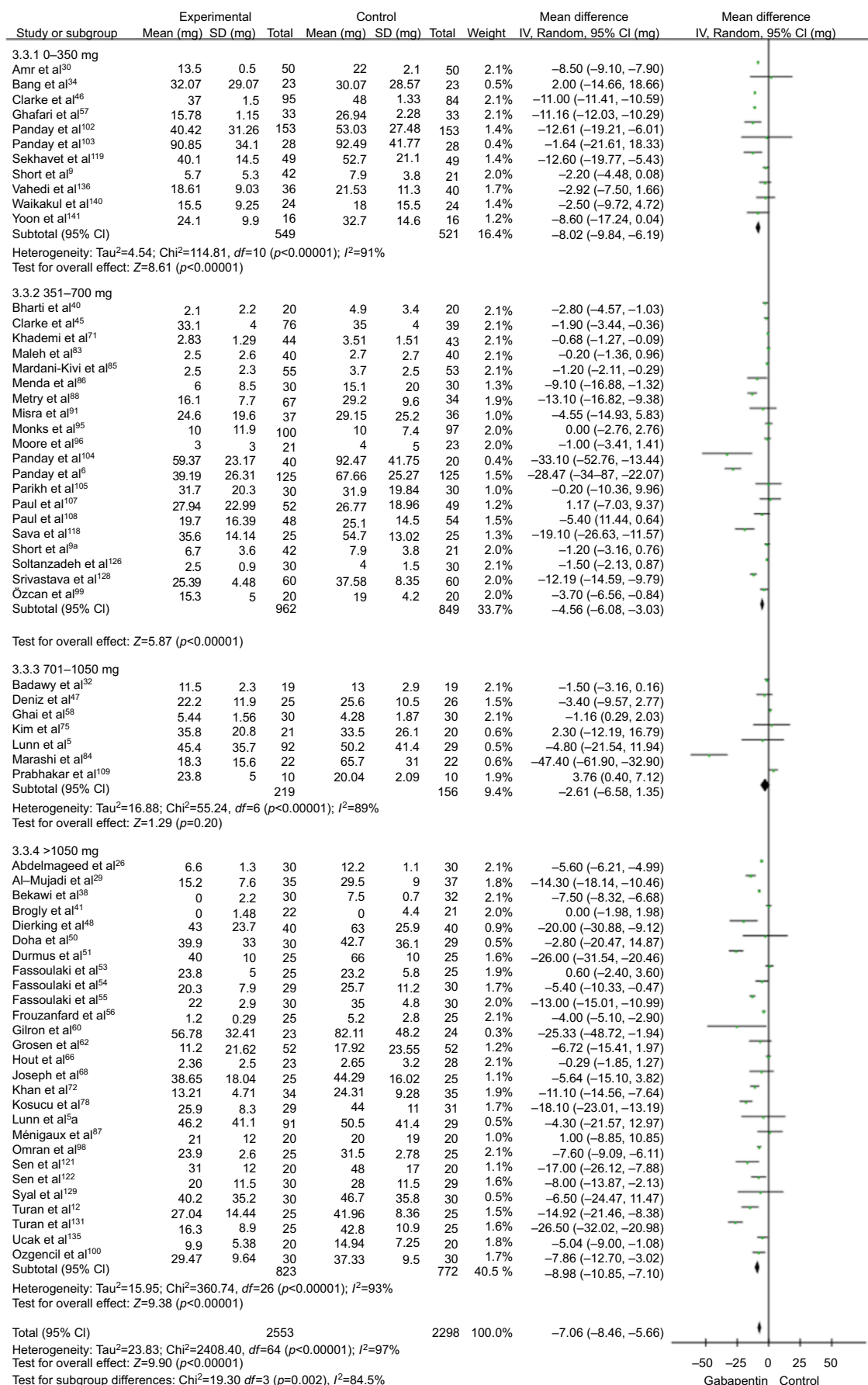


Figure 3 Forest plot of 24-hour morphine consumption from all trials estimates regardless of bias evaluation.

Abbreviations: *df*, degrees of freedom; CI, confidence interval; SD, standard deviation; IV, inverse variance.

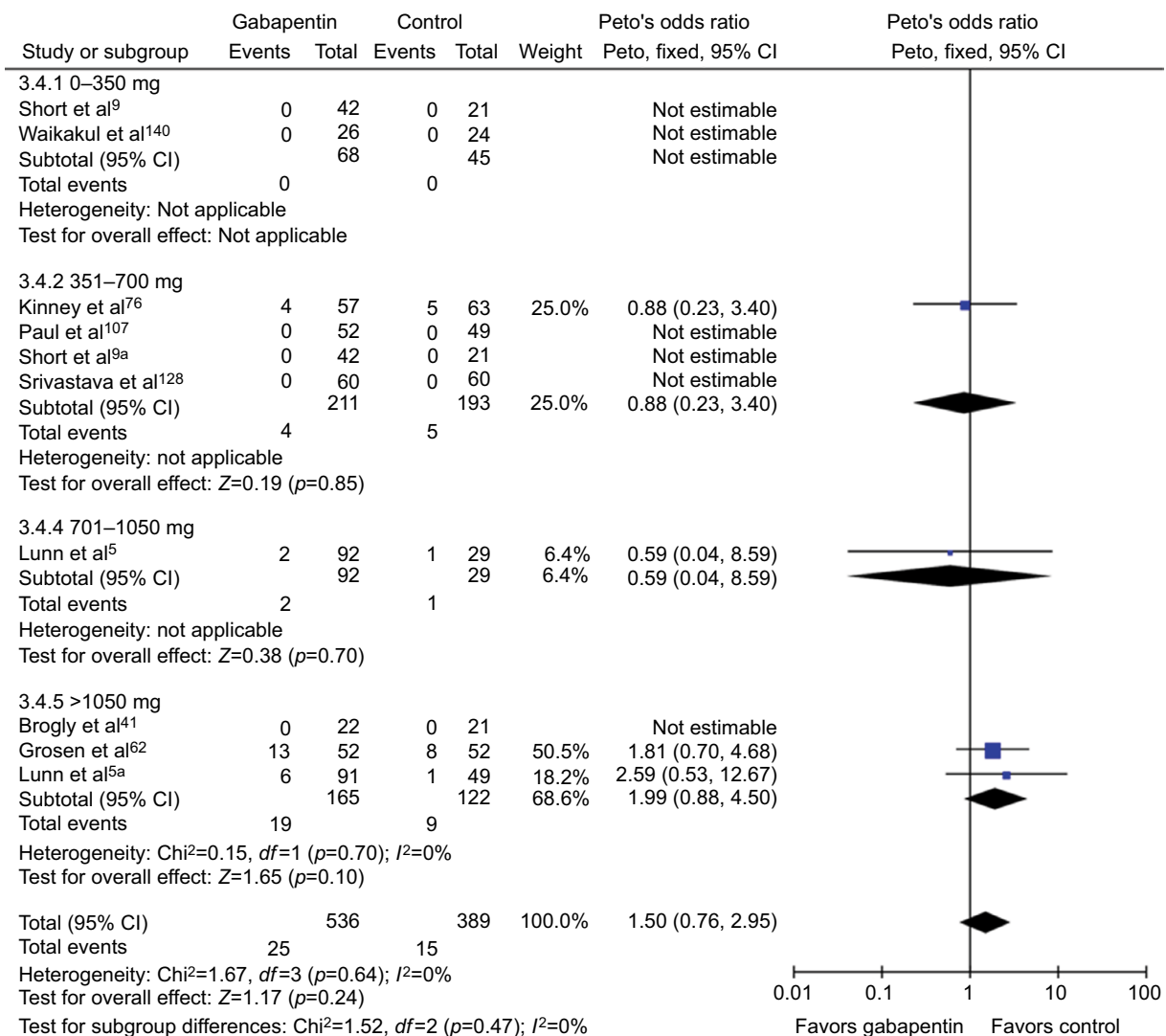


Figure 4 Forest plot of the odds of serious adverse events from trials with overall low risk of bias.

Abbreviations: df, degrees of freedom; CI, confidence interval.

Acknowledgments

These are post hoc subgroup analyses from a systematic review with meta-analyses and trial sequential analyses: Fabritius ML, Geisler A, Hansen MS, Nikolajsen L, Hamunen K, Kontinen V, Wetterslev J, Dahl JB, Mathiesen O. Gabapentin for post-operative pain management – a systematic review with meta-analyses and trial sequential analyses. *Acta Anaesthesiol Scand*. 2016;60:1188–1208.

We would like to thank Sarah Louise Klingenberg, Trial Search Coordinator at Cochrane Hepato-Biliary Group for the extensive literature searches; and Morten Sejer Hansen, MD, Department of Anaesthesiology, Centre of Head and Orthopaedics, Rigshospitalet, Copenhagen University Hospital, Denmark; Lone Nikolajsen, DMSci, Professor,

Department of Anaesthesiology, Aarhus University Hospital, Denmark; Anja Geisler, RN, Department of Anaesthesiology, Zealand University Hospital, Køge, Denmark; and Pernille Lykke Petersen, MD, PhD, Department of Anaesthesiology, Centre of Head and Orthopaedics, Copenhagen University Hospital, Rigshospitalet, Denmark, for their help in data extraction.

The project was supported by departmental funding from the Department of Anaesthesiology, Centre of Head and Orthopaedics, Copenhagen University Hospital, Rigshospitalet, Department of Anaesthesiology, Bispebjerg and Frederiksberg Hospitals and Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen University Hospital, Rigshospitalet.

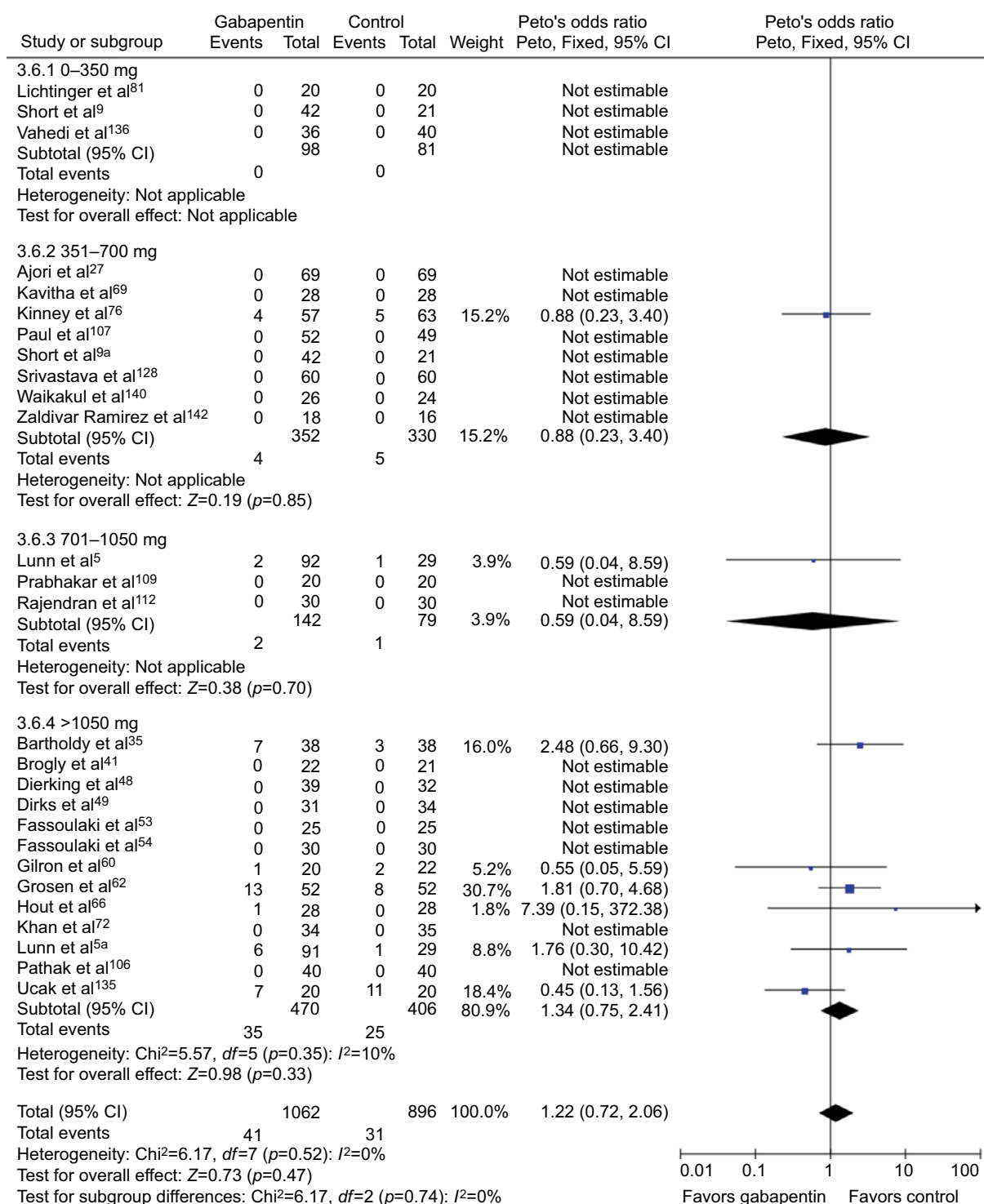


Figure 5 Forest plot of the odds of serious adverse events from all trials estimates, regardless of bias evaluation.
Abbreviation: df, degrees of freedom.

Author contributions

All authors meet the criteria, ICMJE recommendations for authorship and have made substantial contributions to conception and design, acquisition of data, or analysis and

interpretation of data, have revised the article critically for important intellectual content, and have given their final approval of the version to be published. All authors have agreed to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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